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What is an organism? An immunological answer

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Abstract

The question "What is an organism?", formerly considered as essential in biology, has now been increasingly replaced by a larger question, "What is a biological individual?". On the grounds that i) individuation is theory-dependent, and ii) physiology does not offer a theory, biologists and philosophers of biology have claimed that it is the theory of evolution by natural selection which tells us what counts as a biological individual. Here I show that one physiological field, immunology, offers a theory, which makes possible a biological individuation based on physiological grounds. I give a new answer to the question of the individuation of an organism by linking together the evolutionary and the immunological approaches to biological individuation.

1. Introduction

The question "What is an organism?", formerly considered as essential in biology (e.g. Huxley 1852, Haeckel 1866, Loeb 1916, Goldstein 1939, Medawar 1957, Wolvekamp 1966, Lewontin 1983), has now been increasingly replaced by a larger question, "What is a biological individual?" (Hull 1978, 1992; Buss 1987; Wilson 1999; Sober 2000; Gould 2002; Wilson 2004). To understand why, we need to define what an individual in general is, and then what a biological individual is. First, what is an individual from a general perspective? It is critical to understand that not every particular is an individual. A particular is everything that can be designated through a demonstrative reference (*this* F). An individual is a particular

which, in addition, is separable, countable, has acceptably clear-cut spatial boundaries, and exhibits transtemporal identity, that is, the capacity to remain the "same" while changing through time (Chauvier 2008). Two aspects of this definition are worth emphasizing. First, "individual" can refer to natural objects (rocks, plants, etc.), as well as to artifacts (tables, cars, etc.). Second, individuality is a matter of degree: a car is better individuated than a cloud, which itself is better individuated than a nose. Of course, other definitions of the term "individual" may be suggested, but the one given here is general enough to reflect the long history of the ontological questions dealing with individuality, at least since Aristotle.

What, now, is a *biological* individual? It is an individual that lives. There is no consensus on what the frontier between living and non-living individuals is, but, for the sake of the argument developed here, we can consider that biochemical complexity, metabolism, and reproduction are good candidates as characteristics of living individuals. Raising the question of biological individuality amounts to asking what the living individuals are in our world. To this question, the commonsensical answer is that organisms are. By "organism", commonsense means a functionally integrated living thing. The living world seems to be made of trees, flies, mice and men, all of which are considered as individuals – indeed, even paradigmatic individuals.

Yet, in the last three decades, several philosophers of biology, most prominently David Hull (e.g. Hull 1992), have argued that: i) it is by no means self-evident to individuate organisms; ii) the notion of a "biological individual" is much larger than that of an "organism": organisms might be biological individuals, but all biological individuals are not necessarily organisms; iii) individuation is theory-dependent; iv) the only biological theory sufficiently articulated to make biological individuation possible is the theory of evolution by natural selection; v) the organism is only one level in the hierarchy of biological individuals, which may include genes, molecules, cells, organisms, groups and species (Hull 1992).

In this paper, I want to show that the organism is not simply one level in the hierarchy of biological individuals, but the most clearly individuated of all biological individuals. I accept (i), (ii)[1] and (iii), but I reject (iv) and, as a consequence, (v). I argue that at least one physiological field, namely immunology, offers a theory of biological individuality. I then articulate immunological individuation with evolutionary individuation. I conclude that, among biological individuals, the organism expresses the highest degree of individuality.

1. Phenomenal individuation

What are the biological individuals in our world? We can think of three ways to individuate biological entities:

i) A phenomenal way, according to which we can easily "see" biological individuals.

ii) A physiological way, according to which the biological world is made of a sub-class of biological individuals, that is, organisms, which are described as functionally integrated units, undergoing continuous change, and made of causally interconnected elements.

iii) An evolutionary way, according to which it is the theory of evolution by natural selection that tells us what a biological individual is.

Let's first examine the phenomenal way. According to this sort of individuation, we can easily determine what the biological individuals are, simply because we can see them. Biological individuals are organisms, and organisms are easy to see in the world. In the same way a table is considered as a good example of an artificial individual, a horse or an ox will be considered as good examples of biological individuals. People who adopt this conception follow a commonsense view of biological individuals. The underlying idea is that we

[1] As the majority of philosophers involved in this discussion, I disagree with (Buss 1987), who equates the individual and the organism, and with (Wilson and Sober 1989), who consider the individual as a special case of an organism.

certainly don't have a very precise definition of the organism, but we don't really need one, because we can all recognize organisms when we see them.

The problem is that phenomenal individuation simply does not work as soon as one considers living things other than higher vertebrates. Commonsense cannot say where the individual is when the focus is on siphonophores, aspens, fungi or slime molds – to take but few examples (see especially Hull 1988, Wilson 1999 and Wilson 2004 for several other examples). What is more, a cell, for instance, fulfils very well all our criteria of individuality, raising the important question of whether a multicellular organism is better seen as one individual or a community of (cellular) individuals. As (Hull 1992) puts it, "commonsense is strongly biased by our relative size, duration, and perceptual abilities" (Hull 1992; see also Lewontin 2000: 76-77).

If we cannot trust our perception, how to determine what the biological individuals are? Following, here again, Hull, we can say that scientific theories constitute an excellent guide: scientific theories, in all natural sciences, offer an ontology, that is, they tell us what the entities of our world are (atoms, fields, genes, etc.) In other words, individuation in science is always theory-dependent (Hull 1992). Moreover, we have good reasons to trust scientific theories, because they can explain and predict what happens in the world much better than commonsense. Certainly the philosopher should not trust blindly what science says about our world, but she should see science as one excellent starting point, with theories as the best of all starting points.

The next step in the reasoning is where I depart from Hull's thesis. Before explaining why I disagree with Hull, I would like to sum up his point. According to Hull, the only true, highly structured and well articulated biological theory is the theory of evolution by natural selection (TENS) (Hull 1992). Therefore, the TENS is our best guide, or even our only guide, when we seek to determine what biological individuals are. Hull emphasizes that physiology or

morphology would be very useful to determine what a biological individual is, *if only* they were grounded in a theory. Unfortunately, the argument goes, there is no such thing as a physiological or morphological theory, and therefore we are supposedly left only with the TENS to individuate biological entities:

> The trouble with Haeckel's solution to the problem of biological individuals is that morphology and physiology do not provide sufficiently well articulated theoretical contexts. Biologists have been engaged in the study of anatomy and physiology for centuries, but no "theories" of morphology and physiology have materialized in the same sense that evolutionary theory is a "theory". In order to see the dependence of individuality on theories, one must investigate more highly articulated areas such as evolutionary biology. (Hull 1992: 184).

Let's now examine evolutionary individuation, then we will get back to physiological individuation.

2. Individuation by the theory of evolution by natural selection (TENS)

If individuation is always theory-dependent and if the TENS is the main, or sole, biological theory, then the best way to individuate biological entities is to determine what an *evolutionary* individual is. Therefore, in the massive literature on this subject, determining what a biological individual is amounts, most of the time, to determining what an evolutionary individual is.

So, what is an evolutionary individual? The answer is given by the structure of the TENS. A biological individual is an evolutionary individual, that is, any entity on which natural selection acts. It is defined by the following characteristics, derived from the structure of the TENS: variation, heredity, differential fitness (Lewontin 1970). In this view, a gene, a genome, an organelle, a cell, an organism, or even a group or a species can all, in appropriate circumstances, be defined as biological individuals. This is called the "hierarchical" conception of evolution (Lewontin 1970, Buss 1987, Gould and Lloyd 1999, Michod 1999,

Gould 2002). According to this conception, the organism is only one biological individual among many others.[2]

But the hierarchical view of biological individuality goes further. It leads to a revision of our ontology. We thought that the biological world was made of organisms as we see them, but this is simply not true, and it is individuation by natural selection that brings this to light. Janzen (1977) typically illustrates this attitude. He argues that while phenomenal individuation apparently tells us that a dandelion is that green thing in our garden, evolutionary individuation tells us that, in real fact, it is the extended, long-lived clone of dandelions that constitutes the biological individual, because it exhibits "reproductive fitness". The consequence is that "there may be as few as four individual dandelions competing with each other for the territory of the whole of North America" (Dawkins 1982: 254). Equally, the aphid evolutionary individual is the set of insects originating from the same egg and "growing" by parthenogenesis. Because they share the same genome, they cannot be said to compete with each other, and they constitute the "parts" of the same individual.

Let's now examine the foundations, and also the difficulties, of physiological individuation.

3. Physiological individuation

Here "physiology" is broadly defined as all the biological fields which deal mainly with "how?" questions, in contrast with "why?" questions, which are raised by *evolutionary* biology. Physiology includes, in particular, anatomy, morphology, most of molecular biology (including molecular genetics), and most of developmental biology (Boron 2005). What I call physiology here was referred to as "functional biology" by Mayr (1961), but I prefer avoiding the phrase "functional biology" because the etiological conception of functions points towards

[2] A more radical view is that the living world is, from a scientific point of view, made of genes, and not of organisms. This view, held by (Dawkins 1982), may lead to the idea that "there is no such thing as an organism", as discussed by Sterelny and Griffiths (1999: 70). What follows will make clear why I think this view is utterly wrong.

evolutionary biology. Of course, physiology and evolutionary biology are complementary, not conflicting, but still most biologists acknowledge that they are more physiology-oriented or alternatively more evolution-oriented in their everyday work.

Physiology tries to make more solid and precise the commonsense conception of what a biological individual is. It says that organisms are indeed the individuals of the living world, but it offers an argument for this assertion. The argument is that the organism is a coherent, functionally integrated, whole, undergoing continuous change, and made of causally interconnected elements. This view, exemplified by Kant ([1790] 2007), dominates physiology.

Many philosophers consider functional integration as a criterion for biological individuation (Wolvekamp 1977; Sober 1991; Sober 2000). I agree it is a very useful criterion, but I think it needs to be made much more precise. I consider that the concept of functional integration is too vague to offer an effective *criterion* for individuation, because it is too close to the phenomenal individuation: we simply trust our impression that the organism is a coherent "whole", which we cut into functional pieces, and to which we attribute "natural boundaries" (like the skin). For example, what are the "natural boundaries" of the colonial organism *Botryllus schlosseri*? Each zooid has a membrane, and is, at least to some extent, an integrated whole, but one could say that the "true" functional integration happens at the level of the colony, which has a common vascular network. What, then, is the proper physiological individual? In organisms like ourselves, a cell is spatiotemporally localized and functionally integrated: what are the criteria that lead us to say that the organism is the "true" biological individual in this case? Functional integration is certainly a good principle, but it needs a more precise account, based on a *criterion* of individuation.

Of course, one solution would be to say that the multicellular organism is an individual made of cells that are also individuals (Sober 1991). But the problem is that, if this were true, then

we would have no reason to believe that the organism is better individuated than a cell – in other words, functional integration would not define *degrees* of biological individuality. What is more, if it were true, physiology would not deal specifically with organisms, but with any functional unit. I think physiology is really about organisms, but needs a precise criterion to demonstrate so. I agree with Hull (1992) that a proper individuation needs a theory. We must therefore figure out whether a criterion of individuality based on a physiological *theory* is possible. In the next section, I show that, if properly understood, one field of contemporary functional biology, immunology, offers a theory of biological individuality.

4. Individuation by a physiological theory: immunity and the biological individual

4.1. What is the relation between immunology and individuation?

Since its inception, immunology has been considered as a key domain for the definition of biological individuality (Metchnikoff 1907; Loeb 1937; Medawar 1957; Burnet 1969; Tauber 1994). Yet what one should understand by this notion of "individuality" remains unclear. Here I use the notion of a *criterion of immunogenicity* to precisely define the contribution of immunology to the problem of biological individuation.

Immunology aims at finding a criterion of immunogenicity, that is, at determining why and when an effective immune response is triggered. An immune *reaction* is a biochemical interaction between immune receptors and antigenic patterns. In certain conditions, an immune reaction can lead to an immune *response*, that is, to immune *activation*, which leads either to the destruction of the target (lytic activity), or to the prevention of such a destruction (downregulatory activity). The immune system, in every organism, exerts a permanent surveillance of the molecular patterns expressed by the entities present in this organism (Dunn et al. 2002). Any entity expressing strongly abnormal patterns will be rejected by the immune

system. A criterion of immunogenicity is precisely an attempt to say what exactly this "abnormality" is. Hence, the immune system, by its surveillance activity, defines what will be accepted, and what will be rejected, by the organism, and therefore a criterion of immunogenicity constitutes a *criterion of inclusion* for the organism: the distinction between the entities which will stick together as constituents of the organism, and those which will be rejected from the organism, is made by the immune system.[3] As a consequence, the immune system is certainly not the same thing as the organism, but it is a sub-system of the organism, the activity of which leads to the discrimination between what is a part of the organism, and what is not. This discrimination happens through time (*i.e.*, it is diachronic): for instance, a proper criterion of immunogenicity must explain why an organism with one kidney at time 1 can have a second, perfectly tolerated kidney, coming from its twin brother, at time 2. Immunity offers a *criterion of diachronic inclusion*, that is, a criterion for what makes the organism a *unit* constituted of different entities through time. The idea that the immune system can explain what the constituents (parts) of the organism are has been intuitively expressed many times (e.g., Gould and Lloyd 1999: 11906). What is needed now is a precise account of how this organismic individuation works.

Naturally, I am not saying that immunology is the only physiological field that can help to give a precise account of organismic individuality. I am saying that immunology is ready to answer Hull's challenge, because it offers a criterion of individuality grounded in a physiological theory. It is very likely that developmental biology, studies of metabolism, studies of phenotypic plasticity, among others, could also play an important role in defining organismic individuality, but I leave to others the task of determining whether or not they can offer a proper theory and hence a proper criterion of individuality.

[3] Of course, other biological activities lead to the *rejection* of some entities. We can think of metabolic activities: nutrition (rejection of faecal matter) and breathing (rejection of CO_2). Nevertheless, by these metabolic activities, the organism *assimilates* something, and rejects the by-product of its own assimilation activity. By contrast, the immune system accepts or rejects living entities (organs, tissues, bacteria, parasites, even viruses – which we consider as living entities) themselves as parts of its identity.

Before examining in details how immunological individuation works, I shall examine a possible objection: aren't there very few organisms in nature that possess an immune system? If this is indeed the case, then how can I claim to build on immunology a general physiological theory of biological individuation, supposed to hold for all organisms?

4.2. The domain of an immunological theory of individuation

My answer is that this is simply not true that only very few organisms (*i.e.*, higher vertebrates) have an immune system. For several decades, immunologists have believed that immunity was limited to jawed vertebrates, because of an illegitimate focus on lymphocytes, seen as the only "true" immune actors. Nevertheless, it is now clear to all immunologists that immunity is ubiquitous (Kurtz and Armitage 2006; Pradeu 2009): in all organisms in which immunologists have looked for an immune system, they have found one, and most of the time a very complex one.

What, then, is immunity? One can talk of an immune system each time one finds specific interactions between receptors and ligands, which can lead to the destruction (lysis) of the target. With such a definition in mind, one finds immunity in all organisms. Let us examine two cases, the well-known insect *Drosophila*, and plants. The *Drosophila* possesses an immune surveillance system, especially thanks to its "Toll" receptors, with which it can sense pathogens (Khush, Leulier and Lemaitre 2002). Interestingly, an equivalent of these receptors exists in mammals, where they are called "Toll-like receptors", and play a key role in initiating immune responses.

Plants have several immune mechanisms, which can be classified according to two lines of defense. The first one is the direct recognition of *pathogen-associated molecular patterns* by plant transmembrane receptors. The second one, called the "indirect" pathway, is the

recognition of specific effector molecules produced by the pathogen. It consists, like mammalian adaptive immunity, in a highly specific recognition of pathogen products. It is mostly triggered by NBS-LRR proteins, that is, proteins encoded by resistance (R) genes and containing a nucleotide-binding site (NBS) and leucine-rich repeats (LRR) (DeYoung and Innes 2006).

Here lies what is probably one of the most important immunological revolutions of the last decade. The clear-cut separation between "adaptive" immunity (sometimes equated with "specific immunity") and "innate" immunity has vanished (Vivier and Malissen 2005). Adaptive immunity was attributed to jawed vertebrates only. Innate immunity was considered to be non-specific, but in fact, from a biochemical point of view, it is specific. Organisms with innate immunity were also said to have no immune "memory", *i.e.* no capacity to mount a more rapid and more efficient immune response in case of a second contact with the same antigen. Yet, here again, many organisms with "innate" immunity have been found to have this capacity (Kurtz and Armitage 2006). The consequence is that today's immunologists admit that the old clear-cut boundary between innate and adaptive immunity is blurred, or even non-existent.

According to an emerging consensus, even unicellular organisms possess an immune system that is, a system of receptors recognizing abnormal patterns. It is a genome's immunity, which can be based on CRISPR (*clustered regularly interspaced short palindromic repeats*) (Barrangou *et al*. 2007), or on similar mechanisms, probably analogous to ARN interference, found in eukaryotes (Plasterk 2002).

Thus, we can conclude that immunity is ubiquitous both in multicellular and in unicellular organisms, and hence that it can be the basis for a general physiological theory of organismic individuation. With these very important precisions in mind, we can now go back to our main

question: what criterion of immunogenicity should we adopt, and how can it be the basis for a physiological theory of individuation?

4.3. Which criterion of immunogenicity should we adopt?

For sixty years now, immunologists have suggested that the proper criterion of immunogenicity consists in the discrimination between "self" and "nonself", and that this discrimination tells us what a biological individual is (Burnet and Fenner 1949, Burnet 1969, Langman and Cohn 2000). I agree that immunology offers a physiological theory of individuation, but I do not consider that this theory can be grounded in the discrimination between self and nonself.

The self-nonself criterion is now increasingly regarded with suspicion (Tauber 1994; Anderson and Matzinger 2000; Pradeu and Carosella 2006a; Greenspan 2007). According to this criterion, an organism does not trigger an immune response against its own constituents, whereas it triggers an immune response against every foreign entity (except, of course, in cases defined as pathological). Nonetheless, recent discoveries in two critical areas, immune autoreactivity and immune tolerance, prove that this criterion is inadequate.

First, lymphocytes that do not react *at all* with "self" constituents of the body simply die. To be selected, both in primary organs and at the periphery, lymphocytes must be continuously stimulated by endogenous antigenic patterns. Furthermore, this normal autoreactivity concerns not only immune interactions, but also immune *effector* mechanisms: for instance, macrophages react to dying "self" cells of the body and eat them (they are the "scavengers" of the body) (Taylor et al. 2005), and regulatory T cells are "self" cells which respond to other "self" cells by downregulating their activity (Sakaguchi 2006).

Second, recent research has shown that immune tolerance is very common. *Immune tolerance* refers to the absence of immune response to foreign entities even if immune interactions with

them occur. In particular, all known multicellular organisms are hosts of many bacteria, parasites, and viruses. For instance, in a human being, commensal and symbiotic bacteria outnumber eukaryotic cells by at least one order of magnitude (Xu and Gordon 2003). Though these foreign entities are sometimes deleterious and can even kill their host, in many cases they are beneficial to the host, and play a functional role. Another example is that the mother does not reject the fetus, though it is genetically different from her.

Instead of the self-nonself criterion, I prefer the "continuity criterion" (Pradeu and Carosella 2006b), according to which every strong molecular discontinuity in the antigenic patterns (whether endogenous or exogenous) with which immune receptors interact induces an immune response. There is a discontinuity if there is a strong modification of molecular patterns with which immune cells interact: to put it very simply, the immune system responds to strongly "unusual" patterns. The criterion is molecular difference, as stated in the self-nonself theory, but not the *origin* of the molecular pattern (*i.e.* endogenous or exogenous), contrary to what is stated in the self-nonself theory.

Immune habituation works both ways: when the immune system responds to an unusual antigen (whether endogenous or exogenous), the second response is usually more rapid and more efficient; but, according to the continuity criterion, when the immune system reacts but does not respond to a usual antigen (whether endogenous or exogenous), the second response is likely to be weaker. This is called induction of tolerance by induction of continuity. Therefore, the repeated presentation of an antigen in non-immunogenic conditions leads to a subsequent tolerance of this antigen. Non-immunogenic conditions are: small quantities of antigen, antigen introduced progressively, and with no proinflammatory signals. Tolerance of microorganisms, feto-maternal tolerance, chimerism, some cases of graft tolerance could all be examples of induction of tolerance by induction of continuity.

The continuity criterion accounts for immune autoreactivity, because it states that immune receptors interact with normal constituents of the body with a medium strength (which is measurable very precisely by its specificity, affinity, and avidity). Interactions are very strong when immune receptors meet unusual patterns. The continuity criterion also accounts for immune tolerance, with the concept of induction of continuity.

Thus, the criterion of immunogenicity we are looking for cannot be the self-nonself criterion, which is grounded in a wrong idea, the preservation of endogenous elements by the immune system of the organism. By contrast, the continuity criterion integrates autoreactivity and tolerance; it offers an experimentally adequate account of immune phenomena, and therefore it can be the criterion of inclusion we are looking for.

This criterion of inclusion is derived from a true physiological *theory* of individuation, because i) it is composed of several, hierarchically organized, hypotheses, ii) it applies to all organisms, iii) it explains current data, and iv) it makes new predictions.

The next question is: what does this physiological theory of individuation tell us about the definition of the organism?

5. The organism, a set of interconnected heterogeneous constituents, interacting with immune receptors

5.1. Definition of the organism

Let us start with the usual physiological definition of an organism: the organism is a functionally integrated whole, which undergoes continuous change, and which is made of interconnected elements, characterized by causal dependence (e.g. Sober 2000). The constituents of John may causally interact with the constituents of Tim, but not with the same intensity, timing, and scale as John's constituents interact with each other. This definition is certainly correct, but it is too general. Biochemistry can help us to make it more precise.

Indeed, though functional integration can be observed at many levels in the organism, the finest level is that of proteins: the parts of an organism (organs, tissues, cells, and even constituents with cells) are indeed interconnected by strong biochemical interactions, involving mainly proteins-proteins interactions (Lesk 2004). In plants, regulation and coordination of metabolism, growth, and morphogenesis often depend on a network of chemical signals (Taiz and Zeiger 2006). In many instances, in multicellular organisms, a cell which does not receive signals from its local environment and which does not send signals to it rapidly dies. The elucidation of protein-protein interactions is a very active field in contemporary biology. It will probably be in the near future the best level to understand functional integration within an organism, because, again, the strength, timing and extension of "inner" biochemical interactions are very different from those occurring between two distinct organisms (Lesk 2004).

The problem is that, even at a biochemical level, functional integration is *local*. In other words, two sub-systems in an organism can be quasi-independent (Lewontin 2000: 94). It is at this point that the contribution of immunology is critical: immune interactions are fundamentally *organismic* (*i.e.* they concern the whole organism), because they are *systemic*, for the lymphatic system (or its equivalent) is an extensive system, collecting extracellular fluid (lymph) from all tissues of the organism. All the tissues and cells of the organism are therefore under the influence and control of the immune system.

Thus, immune interactions are a sub-set of biochemical interactions, but: i) they are *systemic* (as opposed to local), ii) they offer a *criterion* of inclusion, because they are responsible for the acceptance or rejection of constituents in the organism. Now we reach the heart of the argument. When we link together the general biochemical point of view and the specific but systemic immunological point of view, we obtain the following definition of an organism:

An organism is a functionally integrated whole, made up of heterogeneous constituents that are locally interconnected by strong biochemical interactions and controlled by systemic immune interactions that repeat constantly at the same medium intensity.

It should be clear that the immune interactions are critical in this conception and that they constitute the basis of our physiological individuation of the organism. First, whereas biochemical interactions are most of the time local, immune interactions are systemic. Second, while the strength of biochemical interactions is not always easy to define (because of their diversity), immune interactions are receptor-ligand interactions, the strength of which is very clearly defined in terms of specificity, affinity and avidity. Immune cells interact in a medium, but not too strong, way with the antigenic patterns of the organism's constituents: if these interactions are very weak, the target (whether endogenous or exogenous) dies; if they are very strong, it means than an immune response, leading to a possible rejection of the target, has been triggered; it is only if they remain at the same intermediate intensity that we observe a normal homeostatic state in the organism. These interactions must also be repeated continuously (constantly), which means regularly, and not, of course, without any interruption.

My definition does not imply that everything which does not trigger an immune response from an organism belongs to this organism: for instance, two identical twins can tolerate each other's organs in case of transplantation, but it does not entail that they are one and the *same* organism. Instead, my criterion requires both presence and inclusion (absence of rejection).

I also believe that my definition sheds some light on the frequently made assertion that every organism is "heterogeneous" (Lewontin 2000).

5.2. The heterogenity of the organism

According to my definition, the constituents of an organism are *heterogeneous*. The word "heterogeneous" is not synonymous with "different", it etymologically means "coming from the other", that is, in this context, coming from what is initially the "outside" of the organism. My discussion of immune tolerance has shown the importance of this heterogeneity: an organism is made of constituents that do not need to have originated *in* it. In other words, an organism is made of many foreign things, it is never endogenously constructed. I can illustrate this heterogeneity by an examination of the *functional* role of indigenous symbiotic bacteria in mammals (Hooper and Gordon 2001). For example, each human being is constituted of indigenous symbiotic bacteria that clearly outnumber his or her "own" cells, originating from the egg cell. The majority of these bacteria live in our intestine. Most of them are obligatory symbionts, meaning that they cannot survive outside the host, and the host cannot survive in their absence. They play indispensable physiological (functional) roles: in particular, gut bacteria are needed for digestion. Strikingly, these symbiotic bacteria, far from being foreign enemies that our immune system should fight, also play an indispensable immune role in our bodies (Noverr and Huffnagle 2004). These bacteria have permanent and constitutive biochemical interactions with other parts of the host. There is no fundamental difference between interactions of the host's immune receptors with these symbiotic bacteria, and interactions of the host's immune receptors with endogenous constituents. In both cases, what we observe is a *regulated immune reactivity*. Consequently, these endosymbiotic bacteria are not just "here" in the organism, they are *parts* of the organism (O'Hara and Shanahan 2006; Xu et al. 2007). An objection could be that the gut is an interface of the organism, not a true "internal" part of it. Nevertheless, of the ten mammalian organ systems, eight (integumentary, digestive, respiratory, excretory, reproductive, immune, endocrine, circulatory) have persistent associations with normal bacteria (the exceptions being, so far, the musculoskeletal

and nervous systems) (McFall-Ngai 2002). The organism is a "local concentration of interfaces" (Patrick Blandin, personal communication).

Obligate indigenous bacteria are in no way limited to mammals, we find them in arthropods, plants, colonial organisms, etc. For example, *Wolbachia* bacteria, which are present in many multicellular organisms, have been proved to be indispensable for the development of a parasitic wasp, *Asobara tabida* (Dedeine et al. 2001). In many plants, too, some bacteria are indispensable for nutrition, as illustrated by the symbiosis between the host plant and the bacteria *Rhizobium* (Kiers et al. 2003).

Thus, every organism is a heterogeneous entity, made of different constituents from different origins, but unified by common interactions with immune receptors. As a consequence, a proper criterion of immunogenicity tells us first that the organism is a unified whole (its unity is grounded in biochemical and above all in immunological interactions), and second that it is heterogeneous. It offers therefore a dialectical understanding of the "inside" of the organism (Lewontin 1994): some entities usually considered as parts of the environment are in fact constituents of the organism's identity.

5.3. Biological genidentity defined thanks to immune interactions

The definition of the organism suggested here gives a precise content to the notion of genidentity as applied to biological entities (Locke ([1975] 1690); Lewin 1922; Reichenbach 1956; Hull 1992). The genidentity thesis asserts that individuality through time is insured by the spatiotemporally continuous interactions among the constituents of a being. A classical objection is that it is impossible to speak of interactions among constituents without saying *to what* these interactions must be attributed, and hence without considering that a "core" (substratum) underlying these interactions must exist. Nevertheless, this objection can now be rejected: the immunogenicity criterion allows us to single out the biochemical interactions

that are constitutive of the organism as a whole. The (constantly repeating at the same medium intensity) immune interactions single out continuous biochemical interactions, which themselves single out the organism.

My definition does not start with the constituents of an organism, and then asks what the interactions between them are. It states that every entity bearing molecular patterns that continuously trigger immune interactions of medium intensity is a constituent of the organism. What is fundamental, therefore, is the strength of the immune interactions, which tells us what the constituents of the organism are (e.g., endobacteria).

5.4. Difference with other physiological ways to individuate biological entities

The immunological-physiological individuation I suggest differs from both commonsense physiological individuation, and endogenous physiological individuation.

First, my conception is grounded in the usual physiological definition of the organism (functional integration), but it certainly does not amount to the commonsense physiological individuation, which states that the organism is what is behind the skin (or any membrane). Let us go back, for instance, to the colonial organism *Botryllus schlosseri*. In this case, as we saw, commonsense individuation cannot say what the proper biological individual is, between the zooid and the colony. My criterion of individuality tells us that the organism in this case is not each zooid, but the colony characterized both by strong biochemical interactions and by a one and the same immune system, based on one histocompatibility system (maintained from the larva stage to the colony stage) (De Tomaso et al. 2005). Sometimes, my criterion gives the same result as the commonsense view, but it offers a scientific ground for this result: for instance, my criterion tells us that a mouse as we see it is indeed an individual organism, but, contrary to the commonsense view, it also states precisely what counts as a *part* of the mouse. Counterintuitively, gut bacteria, bacteria situated on the skin, long-tolerated parasites, etc. are

part of the mouse. Thus, again, I offer a proper theory, leading to ontological revisions or confirmations.

Second, my criterion shows that the usual conception of the organism as an endogenous entity is wrong. The idea that the organism is the set of constituents originating from the egg cell, *i.e.* a genetically homogenous entity, is often expressed (e.g. Hull 1978). Immunological individuation shows, however, that every organism is heterogeneous – made of entities of different origins.

In the last section, I try to articulate the two theoretical criteria (the immunological-physiological one and the evolutionary one), and to show what the consequences of this articulation are.

6. Articulating the physiological and the evolutionary individuations

We now have two theories with which to individuate biological entities. According to the evolutionary criterion, there exists a hierarchy of individuals, the organism being simply one of them. By contrast, my physiological criterion shows that the organism expresses the highest level of individuality among biological individuals, for the three following reasons.

6.1. The boundaries of the "heterogenous organism" are clearly defined

Part of Hull's argument is that the organism does not possess clear-cut boundaries (Hull 1992). It is true with the phenomenal definition of an organism, but not with the one given here. The immunological criterion of individuation allows us to take decisions, as in the case of *Botryllus*. I do not pretend that this criterion eliminates all contentious cases, but I do claim that the organism as I define it has more clear-cut boundaries than the other levels in the evolutionary hierarchy, in particular a gene (Griffiths and Stotz 2006) or a group.

6.2. The "heterogenous organism" is sometimes the proper evolutionary individual

Let us go back to clonal organisms, and especially to Janzen's aphids (Janzen 1977). His point is that, during the parthenogenesis phase, the aphid organism (the observable insect) is not an evolutionary individual. Instead, the evolutionary individual is the set of all the insects originating from the same egg, because they all have the same genome, and cannot be said to compete with each other. The underlying idea, more or less inherited from Weismann, is that genetic homogeneity is the key to evolutionary individuality.

The immunological-physiological criterion, however, suggests something else. Each immunological-physiological aphid[4] contains intracellular symbionts, whose presence is required for the survival of the host. These symbionts are vertically transmitted (each aphid transmits its symbionts to its offspring). They are different in different aphids. They can mutate during the aphid lifetime, modify its fitness, and that of its offspring (O'Neill et al. 1997). For example, Dunbar et al. (2007) show that a point mutation in *Buchnera aphidicola*, hosted by *Acyrthosiphon pisum* aphid, modifies the host response to heat stress, "dramatically affecting host fitness in a manner dependent on thermal environment". It means that physiological aphids born by parthenogenesis do in fact compete with each other: they contain endosymbionts which vary, whose variation is inheritable, and modifies host fitness. The aphid case shows that the argument of genetic homogeneity can lead to wrong conclusions about what the evolutionary individual is. I defend an extended replicator view, stating that genes are not the only replicators in nature (Sterelny et al. 1996). Indeed, vertically-transmitted bacteria can be excellent replicators, too.

My argument concerning aphids probably holds for most clonal organisms, especially plants, which massively host obligate symbiotic bacteria (Kiers et al. 2003) or fungi (van der Heijden et al. 1998), though the mode of transmission (vertical or horizontal) makes a difference. For

[4] Following our definition, an immunological-physiological aphid is a small aphid insect, including its indigenous bacteria, fungi, etc.

instance, it is likely that my argument can be made for dandelions. If this is true, it will revise Janzen's revision of the ontology of living entities: in many clonal organisms, the evolutionary individual would not be the clone, but the immunological-physiological organism. Hence, what counts as an evolutionary individual should not be determined by resorting to the sole criterion of genetic homogeneity. A precise observation of physiological, and especially immunological, mechanisms is needed. I do not claim that the organism as I define it is *always* the proper evolutionary individual, but that it is often necessary to start with the heterogeneous organism to determine what the evolutionary individual is, especially in all cases where endobacteria are vertically transmitted.

I think that this conclusion extends the ideas of Leo Buss. Buss (1987) used a physiological domain, developmental biology, to show that the conception of the organism as a genetically homogenous entity was (approximately) correct only in a very limited number of species. He showed that many organisms are heterogeneous in the sense that, contrary to Weismann's main idea, their somatic cells can mutate and subsequently give rise to germ cells. Here I use another physiological domain, immunology, to show that many organisms are heterogeneous in the sense that some of their constituents do not come from the egg cell and can be transmitted to their offspring and influence their fitness. Even organisms Buss considers as "homogenous", e.g. arthropods, are in fact heterogeneous, because they are constituted of entities of different origins, which can influence their evolution.

6.3. The "heterogenous organism" controls the variations of lower-level constituents, especially cell lineages

The emergence of the pluricellular organism in evolution presupposed the existence of mechanisms controlling the appearance of lower-level variants, especially at the level of cell lineages (Buss 1987). The immune system plays a critical role in this control (Buss 1987;

Michod 1999), which is exerted on cell lineages, but also on endobacteria (Frank 1996). As we saw, immune surveillance is exerted towards all the constituents of the organism. The immune system constantly eliminates "selfish" cell lineages, in the case of tumors in particular. The immune system constantly maintains the individuality of the organism by eliminating the replication of lower-level individuals. Naturally, it is possible that natural selection at a higher level (e.g. group or species) presupposes that variations at the organismic level should be restricted, but this control is not as regular and as efficient as in the case of the organism controlling its lower-level constituents.

7. Conclusion

Immunology makes a physiological theory of individuality possible. A proper criterion of immunogenicity offers an account of what the parts of an organism throughout its life are. An organism can be defined as a functionally integrated whole, made up of heterogeneous constituents that are locally interconnected by strong biochemical interactions and controlled by systemic immune interactions that repeat constantly at the same medium intensity. When articulated with the evolutionary criterion of individuation, this physiological criterion shows that the heterogeneous organism is not simply one level in a rich hierarchy of biological individuals, but expresses the highest level of individuality among all living things.

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